W3099

# Development and *In Vivo* Pharmacoscintigraphic Evaluation of a Novel Triple-Release Dexmethylphenidate Hydrochloride Tablet for Improved Once Daily Dosing


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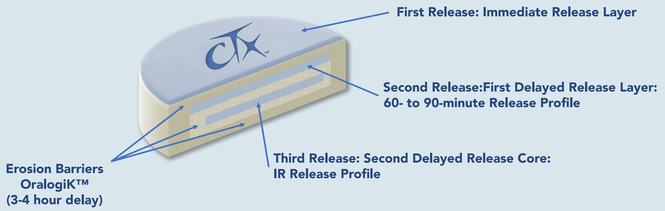
## PURPOSE

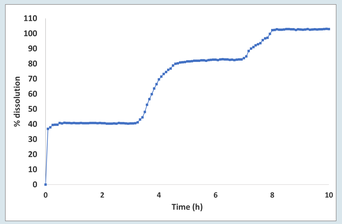
To design a novel triple-release dexmethylphenidate hydrochloride (d-MPH) tablet for once daily ADHD therapy with extended therapeutic plasma levels utilizing OralogiK™ technology, assess *in vivo* performance using pharmacoscintigraphy, and compare pharmacokinetics with commercially available Focalin XR.




## METHOD(S)

A fasting, three-arm pharmacoscintigraphic study in healthy male volunteers compared the pharmacokinetics of the 12.5 mg CTx 1301 triple-release tablet and 10-mg Focalin XR capsules.

Subjects received a single dose of the appropriate treatment at approximately 9 AM on each treatment day. CTx-1301 tablets were validated with the following *in vitro* release profile:




- Treatment A: Commercially obtained 10-mg Focalin XR capsules (not radiolabelled)
- Treatments B & C: 12.5-mg CTx-1301 tablets radiolabelled (4 MBq technetium-99m) to visualise site and time of *in vivo* release (second or third release layers of the 12.5-mg CTx-1301 tablets)
- Subjects received one dose of each treatment under fasting conditions with dosing separated by a minimum of 7 days
- Sequential anterior and posterior abdominal images of 25 seconds duration were acquired using a Siemens eCam every 20 minutes until 14 hours post-dosing; pharmacokinetic blood sampling was carried out at defined intervals
- Plasma profiles were compared to time and site of radiolabel release for the 12.5-mg CTx-1301 tablets, and dose corrected pharmacokinetic parameters were compared across all formulations

## RESULT(S)

Radiolabelled 12.5-mg CTx-1301 tablets demonstrated:

- Mean onset of radiolabel release for the second d-MPH release was at 4.7 ± 1.3 hours; excellent correlation with $Tmax_{(4-8)}$ (5.8 ± 1.2 hr) for the second d-MPH release for Treatment $B_{(4-8)}$
- Mean onset of radiolabel release for the third d-MPH release was at 10.3 ± 1.7 hours; correlates with the higher d-MPH plasma level $AUC_{(8-24)}$ hours

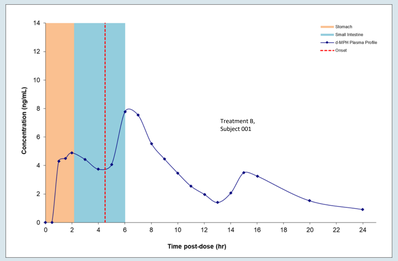



Figure 1 Composite of Treatment B, Subject 001 12.5-mg CTx 1301 d-MPH drug plasma profile with identification of the time/point of radiolabel release from second release layer

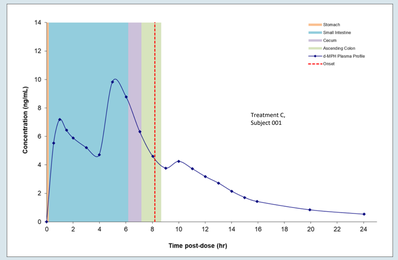



Figure 2 Composite of Treatment C, Subject 001 12.5-mg CTx 1301 d-MPH drug plasma profile with identification of the time/point of radiolabel release from third release layer

Table 1 Comparison of mean d-MPH release PK parameters

| Parameter | Focalin XR (Treatment A) Mean (Range) | CTx-1301 (Treatment B) Mean (Range) | CTx-1301 (Treatment C) Mean (Range) |
|---|---|---|---|
| **d-MPH Release 1**<br>mean $C_{max}$ (ng/mL)<br>mean $T_{max\ 0-4}$(hr)<br>Mean AUC $_{(0-4)}$ | 5.9 (4.2 – 10.4)<br>2.3 (1.0 – 4.0)<br>15.45 (10.4 – 23.8) | 4.9 (2.7 – 7.7)<br>1.6 (1.0 – 2.0)<br>13.3 (7.7 – 20.5) | 5.3 (2.9 – 11.4)<br>1.9 (1.0 – 4.0)<br>14.01 (8.4 – 26.9) |
| **d-MPH Release 2**<br>mean $C_{max}$ (ng/mL)<br>mean $T_{max\ 4-8}$(hr)<br>AUC $_{(4-8)}$ | 7.5 (5.0 – 11.4)<br>5.7 (4.0 – 7.0)<br>22.8 (14.6 – 33.9) | 5.9 (2.2 – 13.0)<br>5.8 (3.9 – 8.0)<br>18.41 (4.6 – 35.9) | 6.3 (2.2 – 11.7)<br>6.3 (5.0 – 8.0)<br>19.75 (7.4 – 33.0) |
| **d-MPH Release 3**<br>mean $C_{max}$ (ng/mL)<br>mean $T_{max}$ (hr) | NA [1] | 2.8 (1.8 – 3.9)<br>13.4 (10.0 – 16.0) | 3.5 (1.7 – 5.7)<br>12.2 (10.0 – 16.0) |
| **Mean**<br>$AUC_{8-24}$ (ng-hr/ml)[2] | 17.1 (10.4 – 34.4) | 29.2 (19.1 – 41.3) | 31.6 (20.5 – 49.3) |
| Mean $AUC_{INF}$ (ng-hr/mL) | 71.25 (52.9 – 117.0) [3] | 63.86 (42.4 – 101.6) | 67.74 (43.6 – 97.2) |

[1]Focalin XR does not Have a Third Release: Focalin data represents the Mean $AUC_{8-24}$ for Focalin for comparison purposes.
[2] Determined by deducting $AUC_{(0-8)}$ from $AUC_{(0-last)}$. [3] Values for Focalin XR normalized to 12.5 mg

- $C_{max}$ data from the IR release (first release) for all three Treatments of the study were comparable at 5.9, 4.9 and 5.3 ng/mL; confirming the initial 12.5-mg CTx-1301 IR layer released d-MPH in a similar manner to 10-mg Focalin XR
- The $C_{max}$ for 12.5-mg CTx-1301 second d-MPH release in Treatments B and C were approximately 20% lower at 5.9 and 6.3 ng/mL respectively when compared to the 10-mg Focalin XR $C_{max}$ of 7.5 ng/mL, an expected result of the CTx-1301 extended second release profile
- The overall extent of absorption of the 12.5-mg CTx-1301 formulations (Treatments B & C) were 89% and 95% of 10-mg Focalin XR
- Mean exposure from 8 – 24 hours as determined by $AUC_{(8-24)}$ values for the 12.5-mg CTx-1301 tablets were significantly higher at 29.2 and 31.6 ng-hr/mL (1.7 – 1.85 greater) than the 10-mg Focalin XR (17.1 ng-hr/mL), confirming the 12.5-mg CTx-1301 tablet design gave higher drug levels for an extended period

Figure 3 shows the d-MPH plasma profiles for Focalin XR (Treatment A), CTx-1301 tablets (Treatments B & C). Figure 4 shows scintigraphic images of the CTx-1301 tablet *in vivo.*

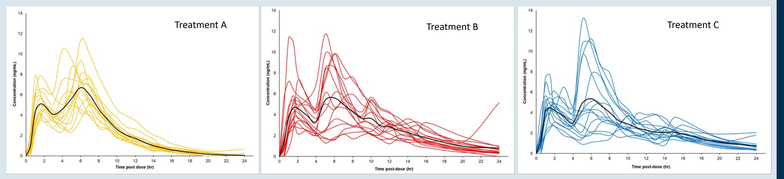



Figure 3 d-MPH plasma profiles for Focalin XR (Treatment A) and CTx-1301 tablets (Treatments B and C)

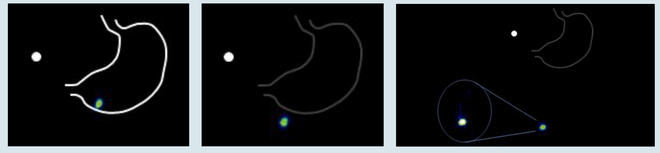


Figure 4 Example of scintigraphic data for 12.5-mg CTx-1301 2nd and 3rd release points (Treatments B and C)

## CONCLUSION(S)

- *The* d-MPH *in vitro* dissolution data correlated well with the *in vivo* release data of radiolabelled CTx-1301 tablets and with pharmacokinetic profiles
- The overall extent of absorption of the 12.5-mg CTx-1301 formulations were 89% and 95% (Treatments B & C) of 10-mg Focalin XR
- The mean IR Layer Release Profile for the 12.5-mg CTx-1301 was similar to the IR Release Profile for the portion of the 10-mg Focalin XR
- The 2nd 12.5-mg CTx 1301 d-MPH release correlated with the CTx predicted delay time and was similar to the 2nd d-MPH 10-mg Focalin XR release
- The 3rd 12.5-mg CTx 1301 d-MPH release extended the plasma levels 4 – 6 hours compared to 10-mg Focalin XR, confirming that the CTx-1301 tablet design strategy offers a potentially new treatment option for ADHD patients

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